UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte AARON J. W. HSUEH, SHEAU YU HSU, SHAN-GUANG LIANG, and PETRUS JOHANNES VAN DER SPEK

Appeal No. 2005-2595
Application No. 09/647,067

ON BRIEF

Before SCHEINER, MILLS, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to nucleic acids encoding a G-protein coupled receptor. The examiner has rejected the claims for lack of utility, nonenablement, and lack of adequate written description. We have jurisdiction under 35 U.S.C. § 134. We affirm the utility and nonenablement rejections and do not reach the written description rejection.

Background

"The receptors for LH [leutinizing hormone], FSH [follicle-stimulating hormone] and TSH [thyrotropin] belong to the large G-protein-coupled, seven-trans-membrane

protein family but are unique in having a large N-terminal extra-cellular (ecto-) domain containing leucine-rich repeats important for interaction with large glycoprotein ligands." Specification, page 1. Appellants refer to G-protein coupled receptors having leucine-rich repeats as "LGR" proteins.

The specification discloses three proteins referred to as LGR4, LGR5, and LGR7. "[T]hese proteins have trans-membrane segments and extra-cellular regions similar to those found in the known LH, FSH, and TSH receptors. In other words, these proteins have both a G-protein coupled seven trans-membrane region and a leucine rich repeat extra-cellular domain." Pages 3-4. "The human LGR7 gene encodes multiple splicing variants, each of which contains a multitude of cysteine-rich low density lipoprotein (LDL) binding motifs at the N-terminus in addition to the l[eu]cine rich repeat regions."

The specification also states that

> [t]he human LGR7 short form gene has a nucleotide sequence as shown in SEQ ID NO:05. The LGR7 short form gene product has an amino acid sequence as shown in SEQ ID NO:06. The human LGR7 long form gene has a nucleotide sequence as shown in SEQ ID NO:07. The LGR7 long form gene product has an amino acid sequence as shown in SEQ ID NO:08.

Page 4. These statements, however, appear to be incorrect. SEQ ID NO:06 is 757 amino acids in length, while SEQ ID NO:08 is 722 amino acids in length. It therefore appears that SEQ ID NOs 05 and 06 represent the long-form LGR7, and SEQ ID NOs 07 and 08 represent the short-form LGR7. This is consistent with the sequences shown in the specification's Figure 3 (LGR7 long variant, SEQ ID NO:05 and SEQ ID NO:06) and Figure 4 (LGR7 short variant, SEQ ID NO:07 and SEQ ID NO:08).

The specification states that the disclosed LGR proteins and nucleic acids encoding them

> find use in a variety of different applications, including the identification of homologous or related genes; the production of compositions that modulate the expression or function of the subject proteins; in the identification of endogenous ligands for the subject orphan receptors; in the generation of functional binding proteins for the neutralization of the actions of endogenous ligands; in gene therapy; in mapping functional regions of the protein; and in studying associated physiological pathways. In addition, modulation of the gene activity in vivo is used for prophylactic and therapeutic purposes, and the like.

Page 2.

"Drug screening may be performed using an in vitro model, a genetically altered cell or animal, purified LGR4, LGR5 or LGR7 proteins, as well as fragments or portions thereof. . . . Areas of investigation include the development of agents that beneficially counter abnormalities related to LGR4, LGR5 or LGR7 and the use of such agents in therapy." Page 20. "Of particular interest in certain embodiments are peptidic agents based on LGR4, LGR5 or LGR7, e.g., solubilized extra-cellular domain or chimeric receptor proteins comprising the LGR4, LGR5 or LGR7 extra-cellular domain, where such agents neutralize the activity of endogenous LGR4, LGR5 or LGR7 ligands, e.g. hormones." Page 21.

Discussion

1. Claim construction

Claims 1, 2, 4, 7-11, and 18-20 are pending and stand rejected. The claims stand or fall together. See the Appeal Brief, page 6. We will focus on claim 1, which reads as follows:

1. An isolated nucleic acid encoding a mammalian leucine-rich repeat-containing G-protein coupled receptor 7(LGR7) protein, wherein the LGR7 protein comprises an amino acid sequence having at least 80% amino acid sequence identity to the sequence set forth in SEQ ID NO:08.

Thus, claim 1 is directed to a nucleic acid that encodes an amino acid sequence at least 80% identical to the short form of LGR7 (SEQ ID NO:08).

2. Utility

The examiner rejected claims 1, 2, 4, 7-11, and 18-20 under 35 U.S.C. §§ 101 and 112, first paragraph, on the basis that the specification does not disclose a patentable utility for the claimed invention.

The examiner bears the initial burden of showing that a claimed invention lacks patentable utility. See In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) ("Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.").

The U.S. Court of Appeals for the Federal Circuit recently addressed the utility requirement in the context of a claim to DNA. See In re Fisher, 421 F.3d 1365, 76 USPQ2d 1225 (Fed. Cir. 2005). The Fisher court interpreted Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966), as rejecting a "de minimis view of utility." 421 F.3d at 1370, 76 USPQ2d at 1229. The Fisher court held that § 101 requires a utility that is both substantial and specific. Id. at 1371, 76 USPQ2d at 1229. The court held that disclosing a substantial utility means "show[ing] that an invention is useful to the public as disclosed in its current form, not that it may be useful at some future date after

further research. Simply put, to satisfy the 'substantial' utility requirement, an asserted use must show that that claimed invention has a significant and presently available benefit to the public." Id., 76 USPQ2d at 1230.

The court held that a specific utility is "a use which is not so vague as to be meaningless." Id. In other words, "in addition to providing a 'substantial' utility, an asserted use must show that that claimed invention can be used to provide a well-defined and particular benefit to the public." Id.

The Fisher court held that none of the uses asserted by the applicant in that case were either substantial or specific. The uses were not substantial because "all of Fisher's asserted uses represent merely hypothetical possibilities, objectives which the claimed ESTs, or any EST for that matter, could possibly achieve, but none for which they have been used in the real world." Id. at 1373, 76 USPQ2d at 1231. "Consequently, because Fisher failed to prove that its claimed ESTs can be successfully used in the seven ways disclosed in the '643 application, we have no choice but to conclude that the claimed ESTs do not have a 'substantial' utility under § 101." Id. at 1374, 76 USPQ2d at 1232.

"Furthermore, Fisher's seven asserted uses are plainly not 'specific.' Any EST transcribed from any gene in the maize genome has the potential to perform any one of the alleged uses. . . . Nothing about Fisher's seven alleged uses set the five claimed ESTs apart from the more than 32,000 ESTs disclosed in the '643 application or indeed from any EST derived from any organism. Accordingly, we conclude that Fisher has only disclosed general uses for its claimed ESTs, not specific ones that satisfy § 101." Id.

In this case, the examiner found that the claimed nucleic acids were not supported by a utility that satisfies § 101 because the "claims are drawn to a nucleic

acid encoding a polypeptide which has an as yet undetermined function or biological significance. . . . In the absence of knowledge of the natural substrate [sic, ligand] or biological significance of this protein, there is no immediately obvious patentable use for it." Examiner's Answer, page 8.

The examiner acknowledged that the specification "teaches that the LGR7 polynucleotide may be useful for producing LGR7 polypeptides, for drug screening of agonists and antagonists, and for neutralizing the action of an endogenous ligand," but concluded that these asserted utilities are not specific or substantial: "The specification . . . discloses nothing specific or substantial about the ligands, agonists/antagonists, and binding proteins that are identified by these methods. Since these asserted utilities are also not present in mature form, so that they could be readily used in a real world sense, the asserted utilities are not substantial." Id., page 7.

We agree with the examiner that the specification fails to disclose a utility that satisfies the requirements of 35 U.S.C. § 101. Appellants argue that the claimed nucleic acids have a well-established utility because "[t]he LGR7 nucleic acids and encoded polypeptides are structurally similar to a small, well-known group of GPCR that bind peptide hormones, e.g., the TSH receptor, the LH receptor, and the FSH receptor. Peptide hormone receptors have a well-established use in the art. Based on the close structural similarity of LGR7 to known peptide hormone-binding GPCR, LGR7 also has a well-established utility." Appeal Brief, page 11.

Along the same lines, Appellants argue that the specification "states that the LGR7 ligand is a hormone" (Appeal Brief, page 12, citing page 21 of the specification) and that "[t]he claimed nucleic acids are thus useful for producing LGR7 polypeptides,

which polypeptides are hormone receptors, and are useful for screening for ligands (e.g., agonists and antagonists), and for the generation of soluble binding proteins for the neutralization of the action of an endogenous ligand. Accordingly, based on the specification, one of skill in the art would readily appreciate the well-established utility of the claimed polynucleotides." Appeal Brief, page 12.

We do not agree that the similarity of LGR7 to known gonadotropin receptors establishes the utility of the claimed LGR7-encoding nucleic acids. We can assume, for the sake of argument, that those skilled in the art would have accepted as accurate the specification's characterization of LGR7 as a leucine-repeat containing GPCR, like the receptors for leutinizing hormone, follicle-stimulating hormone, and thyrotropin.[1]

Thus, it would have been reasonable for those skilled in the art to expect that LGR7 was also a receptor. Based on this expectation, those skilled in the art would have reasonably accepted the specification's statement that certain agents would be "[o]f particular interest," such as "solubilized extra-cellular domain or chimeric receptor proteins comprising the LGR4, LGR5 or LGR7 extra-cellular domain, where such agents neutralize the activity of endogenous LGR4, LGR5 or LGR7 ligands, e.g. hormones."

However, even if these statements would reasonably have been accepted as accurate, they do not amount to disclosure of a patentable utility. Notably missing from the specification's disclosure is any teaching of what specifically LGR7 does. The specification does not disclose what specific ligand is bound by LGR7 or what specific effect would be expected if the ligand were neutralized in vivo. Thus, the specification

[1] The examiner disputes this point, but we need not resolve the dispute in this case.

does not provide sufficient disclosure to allow those skilled in the art to use LGR7, or nucleic acids encoding it, in any specific, real-world use.

In the terminology used by the Fisher court, using LGR7 to make a soluble extracellular domain to antagonize the LGR7 ligand is not a specific or substantial utility. The court held that "to satisfy the 'substantial' utility requirement, an asserted use must show that that claimed invention has a significant and presently available benefit to the public." 421 F.3d at 1371, 76 USPQ2d at 1230. Using LGR7 to antagonize its ligand fails this test because, without further research to identify the ligand bound by LGR7, the skilled artisan would not know what effect to expect from neutralizing that ligand in vivo. Therefore, the specification's disclosure does not provide a "significant and presently available benefit to the public," as required by § 101.

The asserted use is also not specific. The Fisher court held that "in addition to providing a 'substantial' utility, an asserted use must show that that claimed invention can be used to provide a well-defined and particular benefit to the public." 421 F.3d at 1371, 76 USPQ2d at 1230. The disclosure that the extracellular domain of LGR7 can be used to antagonize its ligand, without disclosure of what the ligand is, does not provide those skilled in the art with a "well-defined and particular benefit" because the disclosure does not allow those skilled in the art to do anything specific with the protein.

In the terms used by the Fisher court, the asserted utility of using a solubilized extracellular domain to neutralize the LGR7 ligand could be asserted for any receptor with a ligand-binding domain. Nothing about the asserted utility sets the claimed product apart from other, similar products; therefore, the asserted utility is not specific to the claimed invention.

Appellants argue that the asserted utility is specific, because "[o]ther than LGR-type GPCRs, GPCR typically do not have an amino-terminal ectodomain that can be expressed as soluble proteins and used to neutralize the activity of an endogenous hormone ligand. This particular asserted utility of LGR-type GPCR is thus specific to LGR-type GPCR." Appeal Brief, page 13.

To satisfy § 101's requirement of a specific utility, "an asserted use must show that that claimed invention can be used to provide a well-defined and particular benefit to the public." Fisher, 421 F.3d at 1371, 76 USPQ2d at 1230 (emphasis added). The disclosure that LGR7 can be used to make soluble extracellular domains, which can then be used to antagonize an unidentified ligand, fails this test. Such a disclosure does not provide a well-defined and particular benefit to the public. Instead, it provides merely a basis for further research to determine whether the disclosed protein is useful and, if so, what it can be used for. Using LGR7 to antagonize its ligand, without knowing what the ligand is, does not satisfy the utility requirement of § 101.

Appellants also argue that the utilities asserted in the specification were confirmed by post-filing date evidence.[2] See the Appeal Brief, pages 14-15.

We have considered the post-filing references cited by Appellants to the extent that they confirm the accuracy of statements in the specification. Post-filing evidence cannot be relied on to "render an insufficient disclosure enabling," Brana, 51 F.3d at 1567 n.19, 34 USPQ2d at 1441 n.19, but it may be used to show the accuracy of a statement in the specification. Thus, Appellants can rely on the cited references for the

[2] Appellants rely on Hsu et al. (Hsu (2000)), "The three subfamilies of leucine-rich repeat-containing G protein-coupled receptors (LGR): Identification of LGR6 and LGR7 and the signaling mechanism of

limited purpose of showing the accuracy of the specification's statement that SEQ ID NO:08 encodes an LGR-type GPCR. However, they cannot rely on the substantive disclosures of the post-filing references for the disclosure that, e.g., LGR7 is a relaxin receptor.

Utility is determined as of the effective filing date of the application. See Brana, 51 F.3d at 1567 n.19, 34 USPQ2d at 1441 n.19. Here, the specification disclosed that the protein encoded by the claimed nucleic acids was likely to be an LGR-type GPCR, and this disclosure was confirmed by post-filing evidence. The relevant question with respect to utility, then, is whether a specific and substantial utility for an LGR-type GPCR – having an unknown ligand – was disclosed in the specification or well known in the art as of this application's effective filing date (March 26, 1998).

For the reasons discussed above, we conclude that no specific and substantial utility was disclosed in the specification or would have been apparent to those skilled in the art as of the effective filing date. The rejection of claim 1 under 35 U.S.C. §§ 101 and 112, first paragraph, for lack of utility is affirmed. Claims 2, 4, 7-11, and 18-20 fall with claim 1.

3. Enablement

In addition to the rejection based on lack of utility, the examiner rejected claims 1, 7-11, and 18-20 under 35 U.S.C. § 112, first paragraph, on the basis that it would have required undue experimentation to "make and use fragments and variants of LGR7 that have at least 80% amino acid sequence identity to the sequence set forth in SEQ ID

LGR7," Molecular Endocrinology, Vol. 14, pp. 1257-1271 (2000), and Hsu et al. (Hsu (2002)), "Activation of orphan receptors by the hormone relaxin," Science, Vol. 295, pp. 671-674 (2002).

NO: 8." Examiner's Answer, page 9. The examiner reasoned that, while those skilled in the art would expect many amino acid positions in a protein to be tolerant to substitutions, the specification "provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change . . . and the nature and extent of changes that can be made in these positions." Id., pages 10 and 11. The examiner concluded that when all of the factors set out in In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered, practicing the full scope of the claims would have required undue experimentation. Examiner's Answer, page 12.

We agree with the examiner's reasoning and conclusion. The test of enablement is whether the specification, combined with the knowledge of those skilled in the art, would allow the skilled artisan to make and use the full scope of the claimed invention without undue experimentation. See In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) ("[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'").

In this case, we have concluded that the specification does not disclose any specific and substantial utility for the claimed invention; i.e., that the disclosure would not allow those skilled in the art to use anything within the scope of claim 1. Thus, the disclosure necessarily fails to teach how to use the full scope of the claims.

However, even if the specification disclosed a utility for something within the scope of the claims, we would agree with the examiner that the specification does not

teach those skilled in the art how to use the full scope of the claims. Claim 1 reads on nucleic acids encoding amino acid sequences at least 80% identical to SEQ ID NO:08. The specification does not disclose the biological activity of the protein having the sequence of SEQ ID NO:08, or any domain(s) or specific amino acids of the protein that are important to that activity. In short, the specification provides no guidance that would direct the skilled artisan toward variants that are 80% identical to SEQ ID NO:08 and likely to share the function of LGR7 (whatever that might be).

The guidance provided by the specification amounts to nothing more than an invitation to experiment. While "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed," Wands, 858 F.2d at 737, 8 USPQ2d at 1404, neither of those conditions apply here. As discussed above, the specification does not provide "a reasonable amount of guidance" on the direction in which the experimentation should proceed.

Nor is the experimentation in question merely routine. To practice the full scope of claim 1, those skilled in the art would have to determine which among the myriad possible deletion and substition variants of LGR7 with at least 80% amino acid sequence identity have the same function as full-length, short-form LGR7 (i.e., SEQ ID NO:08). To do so, of course, the skilled artisan would first have to figure out the function of LGR7, because the specification does not disclose even that much guidance. In view of the breadth of the claims, the lack of working examples or significant guidance in the specification, the amount of experimentation that would be

required, and the unpredictability of the art, we agree with the examiner that undue experimentation would have been required to practice the full scope of the invention.

Appellants argue that the specification discloses a variant of LGR7 (specifically, the splice variant represented by SEQ ID NO:06) and a fragment of LGR7 (specifically, the extracellular domain fragment discussed on page 21). Appeal Brief, pages 22-23. Along the same line, Appellants argue that "Hsu (2002), carrying out nothing more than routine experimentation, generated a soluble LGR7 ectodomain, and demonstrated that a soluble extracellular domain of LGR7 functions as an antagonist to LGR7." Appeal Brief, page 25. Appellants also argue that, "[b]ased on the alignments provided in Figure 6, those skilled in the art could readily determine, without undue experimentation, those amino acids of LGR7 that could be altered without changing the function of LGR7." Id., page 23.

These arguments are not persuasive. First, SEQ ID NO:06 (757 amino acids) is longer than SEQ ID NO:08 (722 amino acids long) and therefore cannot be a short-form variant of SEQ ID NO:08. Second, Appellants have pointed to no evidence in the record that shows the extracellular domain fragment contemplated in the specification and discussed by Hsu (2002) is within the scope of claim 1; i.e., evidence that an extracellular domain fragment would comprise at least 80% of the amino acids in the full-length sequence.

Finally, Figure 6 is a comparison of the sequences of LGR4, LGR5, LHR, FSHR, and TSHR. It does not include the sequence of either form of LGR7. Appellants have not adequately explained how a comparison that does not include LGR7 would show

those skilled in the art "those amino acids of LGR7 that could be altered without changing the function of LGR7."

Appellants also argue that, "based on an alignment of the LGR7 amino acid sequence with those of other hormone-binding GPCR," Hsu (2000) made point mutations "in LGR7 that affected its function as a GPCR." Appeal Brief, page 23. Appellants conclude that, "given the information provided in the instant specification, those skilled in the art could readily and without undue experimentation identify and mutate amino acid residues important for the function of an LGR7 polypeptide as a GPCR." Id.

We also find this argument unpersuasive. Hsu (2000) does not provide evidence that the specification would have enabled those skilled in the art to mutate or delete up to 20% of the amino acids in SEQ ID NO:08 and retain the function of the full-length sequence. Indeed, Hsu (2000)'s mutagenesis experiments were not designed to reveal any information about LGR7's ligand-binding activity:

> Although the putative ligands for LGF6 and LGR7 are unknown, studies on single amino acid mutants of LGR7, with a design based on known LH and TSH receptor gain-of-function mutations, indicated that the action of LGR7 is likely mediated by the protein kinase A but not the phospholipase C pathway.

Abstract. Hsu (2000) states that "site-directed mutagenesis . . . provided a novel approach to reveal the signal transduction pathway of selective orphan GPCRs and to facilitate future identification of their cognate ligands." Page 1258, left-hand column.

Thus, Hsu (2000) at best shows that those skilled in the art could have determined which residues of LGR7 were involved in activating protein kinase A activity. Appellants have not adequately explained how these post-filing data show that the

guidance provided in the specification would have enabled those skilled in the art, in 1998, to practice the full scope of LGR7 variants having as little as 80% amino acid identity with SEQ ID NO:08, without undue experimentation.

3. Written description

The examiner also rejected claims 1, 7-11, and 18-20 under 35 U.S.C. § 112, first paragraph, on the basis that these claims are not supported by an adequate written description in the specification. Since we have already concluded that these claims are unpatentable for lack of utility and lack of enablement, however, we need not decide whether they are also unpatentable for lack of adequate description.

Summary

The evidence of record supports the examiner's position that the specification does not disclose a specific and substantial utility for the claimed polynucleotides, or sufficient guidance to enable practice of the full scope of the claimed invention without undue experimentation. We therefore affirm the rejections for lack of utility and nonenablement.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136.

AFFIRMED

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